PCT/FR2003/002996

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WOB99CNRANGI	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/002996	International filing date (*day/month/year*) 10 octobre 2003 (10.10.2003)	Priority date (*day/month/year*) 10 octobre 2002 (10.10.2002)
International Patent Classification (IPC) or national classification and IPC C12N 5/08, G01N 33/50, C07K 16/28, 16/42, A61K 39/395, A61P 35/00, 21/00, 27/00, 19/00, 37/00, 17/00, 9/00		
Applicant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 06 mai 2004 (06.05.2004)	Date of completion of this report 10 February 2005 (10.02.2005)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002996

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-33, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages 1-16, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the drawings:

pages 1/11-11/11, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR 03/02996

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

1. **The amended claims 1-16**, submitted with the letter dated 03.12.2004 do not extend the subject matter of the application beyond the content of the application as filed; they therefore comply with PCT Article 34(2)(b).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

1. Following the invitation to limit the claims or to pay additional examination fees, sent to the applicant on 22.06.2002 by the International Preliminary Examining Authority (IPEA), the applicant has decided to pay part of the additional examination fees and to remove a portion of the claims. The new **claims 1-16** meet the requirements of unity of invention as defined in PCT Article 34(3) and PCT Rules 13 and 68.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3, 7-16	YES
	Claims	4-6	NO
Inventive step (IS)	Claims	1-3, 7	YES
	Claims	4-6, 8-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2: Citations and explanations

1. Reference is made to the following documents:

D1: HUTCHINGS H *et al.*, "Pigment epithelium-derived factor exerts opposite effects on endothelial cells of different phenotypes", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 294(4), 21 June 2002, pages 764-769

D5: WITTE L. *et al.*, "Monoclonal antibodies targeting the VEGF receptor (FLK1/KDR) as an antigiogenic therapeutic strategy", CANCER AND METASTASIS REVIEWS, 17(2), 1998, pages 155-161

Novelty - PCT Article 33(2)

2. The IPEA is of the opinion that the subject matter of **claims 4-6** does not comply with the criterion of novelty (PCT Article 33(2)).

The subject matter of claims 4-6 relates to a polyclonal or monoclonal antibody against endothelial cells of angiogenic phenotype as per claim 1. Since the endothelial cells of angiogenic phenotype according to claim 1 express the VEGFR2

receptor, "an antibody against the endothelial cells of angiogenic phenotype according to claim 1" can be an anti-VEGFR2 receptor antibody. Document D5 describes anti-VEGFR2 monoclonal antibodies that inhibit tumour growth by inhibiting angiogenesis (see, for example, page 157, right-hand column, 2nd and 3rd paragraphs). Therefore, document D5 anticipates the subject matter of **claims 4-6** (PCT Article 33(2)).

It should be noted that the IPEA recognises that the complementary results of Appendix 2 show that the monoclonal antibodies described in the present application and directed against the endothelial cells according to the invention do not bind to the VEGFR2 receptor. However, the subject matter of claims 4-6, as presently worded, is not restricted to these antibodies. It also encompasses monoclonal antibodies that can be directed against the VEGFR2 receptor and that inhibit angiogenesis; in other words, it also encompasses antibodies such as those described in D1. Therefore, said subject matter is not novel.

3. The IPEA is of the opinion that **claims 1-3 and 7-16** comply with the criterion of novelty (PCT Article 33(2)).

3.1. Document D1 describes two types of retinal endothelial cells: the BREC/V cells (cultured in the presence of VEGF) and the BREC/0 cells (cultured without VEGF). The BREC/V cells form tubes in the presence of VEGF in a collagen gel and proliferate under the action of VEGF (see "Materials", page 765, left-hand column, lines 8-11, page 766, left-hand

column, lines 2-5, page 768, left-hand column, lines 10-18). The VEGFR2 expression thereof is identical to that of the corresponding cells of non-angiogenic phenotype (BREC/0) and is lower than that of the cells according to claims 1 and 2 (see page 766, right-hand column, 2nd paragraph, figure 2, and see complementary results in Appendix 1). Consequently, the BREC/V cells described in document D1 differ from those of **claims 1 and 2.**

3.2. The method for preparing angiogenic endothelial cells described in document D1 is characterised by the culture of endothelial cells in the presence of VEGF (see page 765 "Materials"), while the method according to claim 3 is characterised by the culture of endothelial cells in the presence of oestradiol and of VEGF. Consequently, the method described in D1 differs from that of **claim 3.**

3.3. The subject matter of **claims 7-16** cannot be found in the prior art available to the examiner.

Inventive step - PCT Article 33(3)

4. The IPEA is of the opinion that the subject matter of **claims 8, 9 and 10-16** does not comply with the criterion of inventive step (PCT Article 33(3)).

4.1. The subject matter of **claims 8, 9 and 10-14** is directly derived from claims 4-6 and is arrived at via routine technical steps. Consequently, it is not inventive. It could only be considered inventive in combination with a novel and inventive antibody (PCT Article 33(3)).

4.2. The role of angiogenesis in the disease states described in **claims 15 and 16** is already known. Therefore, the use of angiogenesis-inhibiting monoclonal antibodies as per claims 4-6 in the preparation of a drug for treating said disease states is obvious to a person skilled in the art (**claims 15-16**).

5. The IPEA is of the opinion that **claims 1, 2 and 7** comply with the criterion of inventive step (PCT Article 33(3)).

Document D1, which is considered the prior art closest to the subject matter of claim 1, describes endothelial cells of angiogenic phenotype (BREC/V).

The endothelial cells of angiogenic phenotype according to claims 1 and 2 differ from the endothelial cells of angiogenic phenotype as per D1 in that the gene expression thereof is different from that of the BREC/V cells (see complementary results of Appendix 1).

The technical effect resulting from this difference is that the cells according to claims 1 and 2 are capable of generating antibodies having an antitumoral effect.

The technical problem resulting from this difference is that of determining how to produce antibodies with an antitumoral effect.

The solution to said problem, as proposed by the present application, lies in providing the endothelial cells as per claims 1 and 2.

The prior art available to the IPEA does not provide any indication that endothelial cells such as those of claims 1 and 2 are capable of generating antibodies having an antitumoral effect. Consequently, in view of the prior art, it would not be obvious for a person skilled in the art to envisage producing such cells to solve the above problem, i.e. to produce antibodies having an antitumoral effect. Therefore, the IPEA considers that the endothelial cells of angiogenic phenotype as per **claims 1 and 2** and the use thereof as per **claim 7** in the preparation of antibodies having an antitumoral effect, involve an inventive step (PCT Article 33(3)).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. According to the applicant, the method for preparing endothelial cells of angiogenic phenotype as per the present application differs from the method of D1 in that the cells are cultured with VEGF and oestradiol as soon as they are collected, whereas the BREC/V cells of D1 are only contacted with VEGF after 7 passages in the presence of FGF2. The IPEA wishes to point out to the applicant that this feature of the method does not appear in claim 3. Indeed, in its present wording, claim 3 does not specify that the endothelial cells are incubated as soon as they begin to be cultured in the presence of VEGF and oestradiol. Consequently, as it stands, the method according to claim 3 lacks an essential feature required for carrying out said method, i.e. for obtaining the endothelial cells of angiogenic phenotype as per claim 1. Moreover, another essential feature required for carrying out the method is lacking: the composition of the clone culture medium until cell confluency is achieved. Consequently, **claim 3** does not meet the requirements of PCT Article 6, in combination with PCT Rule 6.3(a)(b) (see also PCT Guidelines, C-5-05), which stipulate that an independent claim should contain all the essential technical features required to define the invention.

2. The subject matter of **claims 4, 6, 8 and 9-12** relates in part to an antibody against angiogenesis activating endothelial cells of angiogenic phenotype, to angiogenesis activating anti-idiotypic

VIII. Certain observations on the international application

antibodies directed against said antibodies, as well as to angiogenesis activating anti-anti-idiotypic antibodies. Said subject matter substantially lacks support in the description. Indeed, no result is provided to prove that antibodies capable of activating angiogenesis are obtained. The data in figure 6 only shows that so-called type-5 antibodies stimulate the proliferation of F/0 cells. Said data does not show that the antibodies activate angiogenesis, since no *in vitro* angiogenesis testing has been carried out on the F/0 cells. Likewise, the data does not specify whether said type-5 antibodies are type A, B or C antibodies, i.e. whether they are directed against endothelial cells of angiogenic phenotype or against endothelial cells of non-angiogenic phenotype. Consequently, the IPEA is of the opinion that the part of the subject matter of **claims 4, 6, 8 and 9-12** that is directed to angiogenesis activating antibodies does not meet the requirements of PCT Article 6 and PCT Article 5.